FT SPECIAL REPORT

FT Health

Combating Neglected Diseases

Thursday October 11 2012 www.ft.com/reports | twitter.com/ftreports

Economic reality spurs intervention

Children are tested for sleeping sickness in a WHO screening programme in sub-Saharan Africa Corbis

More is being done to tackle 'NTDs' as research reveals their impact on countries' growth, writes *Andrew Jack*

In remote parts of Congo, Victor Kande struggles to help thousands of people suffering from one of the country's most unpleasant but obscure scourges. He is trying to improve conditions for those with sleeping sickness, one of the most unpleasant of a range of "neglected" tropical diseases.

"Our government has many problems, and all attention is focused on dealing with cholera, Ebola and malaria. Everyone sees and deals with those," says Mr Kande, a health official who struggles with lack of petrol for boats and bikes to reach affected villages. "People with sleeping sickness die slowly in their houses out of sight. It's a rural and social illness that leaves people unable to work, stigmatised and regarded as mad."

He has been working with the Drugs for Neglected Diseases Initiative, a non-profit research group in Geneva trying to improve decades-old medical techniques, which require painful spinal taps for diagnosis and arsenic-based injected medicines that kill a tenth of the patients treated. Sleeping sickness (trypanosomiasis) is one of a number of so-called "neglected tropical diseases" (NTD), dubbed by Dr Peter Hotez, head of the Sabin Vaccine Institute, "the most important diseases you have never heard of." Their names are often unpronounceable, their symptoms almost unimaginable, and their impact on individuals, communities and regional development incalculable.

According to the best statistics available – and the data are extremely poor – more than 1bn people in the world are chronically infected by one or more such NTD, and more than half a million people a year die as a result. Yet they receive scant support for research, prevention or treatment.

Prof David Molyneux at the Liverpool School of Tropical Medicine estimates 0.6 per cent of international development assistance for health goes to NTDs compared with 42 per cent for the "big 3" of HIV, tuberculosis and malaria.

One reason is that they affect the poorest and most disenfranchised, principally in Africa, with little of the visibility in richer nations of diseases which occur in the west. Another is that they often debilitate rather than kill, making their short-term impact less dramatic.

Yet growing research points to the broader consequences of neglect. Soil-transmitted helminthiases (intestinal worms) and schistosomiasis (bilharzia), transmitted through snails, may cause physical stunting, slow intellectual development and impede children's schooling and future ability to work productively.

Onchocerciasis and trachoma cause blindness, a further factor holding back economic development and placing a burden on those who contract the diseases and their families. Greater study of the interaction of animal and human infections has highlighted the impact on agricultural productivity of NTDs.

The good news today is that some are becoming less neglected. Referred to in ancient documents, studied by scientists in the late 19th century, and already dubbed "great neglected diseases" by Ken Warren at the Rockefeller Foundation in the 1980s, they have risen to the priorities of donors and policymakers over the past decade.

There has been a surge in academic articles in the past few years, and even the creation of new journals, such as PlosNTDs. Funding for research into new "tools" has jumped from $268m in 2007 to $460m last year, according to Policy Cures, a think-tank. Donors led by the US Agency for International Development, the UK's Department for International Development and the Gates Foundation have considerably stepped up support.

The activity reached a new peak last January, when 13 pharmaceutical companies signed up to the "London Declaration" on NTDs, offering expanded donations of supplies of drugs with a theoretical commercial value of hundreds of millions of dollars a year that have the potential to prevent and treat many NTDs.

Some stress their corporate responsibility, while others point to economic self interest. "This is a long-term investment in the future middle class," says Haruo Naito, head of Japanese drugmaker Eisai, which pledged to produce diethylcarbamazine for lymphatic filariasis (elephantiasis), in the process expanding its brand name and experience of manufacturing in India and the UK.

Bill Foege, a veteran public health expert, who praises Merck as it celebrates the 25th year of donations of its drug ivermectin for trachoma control this week, says: "This is becoming the way corporations operate. They do not simply do it for good publicity or some sort of tax break, but because when you are competing for good workers, it makes a difference."

He also points to the importance of high-level advocacy among politicians and chief executives inspired by former US president Jimmy Carter, whose tireless efforts mean that dracunculiasis (guinea worm) could by 2015 become only the second human

Continued on Page 2

Inside »

Science is fighting the dengue war on four fronts

Testing occupation: vaccine development at the Sanofi Pasteur site in France
Vincent Moncorgé

Prevention Developing a vaccine against dengue is especially difficult – but potential benefits are enormous, says *Denise Roland*

A breakthrough in tackling the world's most widespread mosquito-borne virus is tantalisingly close, but disappointing results from the latest vaccine trial serve as a reminder of the scale of the challenge.

Dengue, also known as 'break bone fever' due to the excruciating pain suffered by its victims, afflicts 100m people across the globe every year, especially in the tropics.

The disease is on a northward march via a resilient mosquito species arriving in cargo.

The first local transmissions in Europe were recorded in France and Croatia in 2010, and last month Greek health officials attributed the death of an 80-year-old man to its first case of dengue since the 1920s.

No cure exists, so treatment is limited to relieving the agonising bone, muscle and joint pain that accompany the fever. Few cases end in death, but 500,000 people each year develop the severe form. They have a one in 40 chance of dying from its complications, with children at most risk.

Although 2.5bn people are at risk of infection, the disease's low death toll has hidden its impact from the global health community.

Dr Richard Mahoney, policy and access co-ordinator of the dengue Vaccine Initiative, a non-profit organisation, says: "Dengue is different from the other neglected tropical diseases.

"It is a global problem affecting every country in the tropics, and is spreading further – while the others tend to be localised to very specific spots on the globe."

The virus has been on the rise for more than 70 years, but serious efforts by drug companies to create a dengue vaccine – which experts agree would be the single most effective tool in controlling the disease – only gained momentum in the past two decades.

One reason is that the fever can be caused by four different virus strains.

Dr Jean Lang, R&D associate vice-president for Sanofi Pasteur, the company leading the way towards creating a vaccine, says: "Dengue is the only disease with this feature – it's like developing four vaccines for four different viruses.

"If dengue was a simple disease, we would already have a vaccine. It typically takes 10-15 years to bring a vaccine to market – it's an indication of dengue's complexity that it has been nearly 20 years already."

If a new shot fails to protect against one or more of the virus types, more difficulties arise. Some studies have shown that, if a patient becomes immune to one strain, they face increased chances of developing the severe form. It is unclear whether inoculation with the weakened virus in the vaccine would have the same effect.

This stumbling block recently tripped up researchers at Sanofi, who found the candidate they were trialling only protected against three of the four virus types in a trial on 4,002 children in Thailand.

Despite this setback, developers hailed the trial as a milestone in a process started in 1994 when the French pharmaceutical group partnered with a Thai research lab to develop a candidate vaccine.

The intervening 18 years have seen Sanofi become the first company to take a dengue vaccine to late-stage phase III clinical trials.

Dr Lang said that, although the latest results were surprising, the small trial size and the specific conditions in Thailand may mean the results will not be replicated in the much larger phase trials under way on 31,000 people across 10 Asian and Latin American countries.

Sanofi remains confident. With a target of going to market in 2015, it has invested €350m in a factory with the capacity to manufacture 100m doses of vaccine a year.

The growing demand for a dengue jab is attractive for big pharma, with Sanofi forecasting €1bn in annual sales. Others are following, with Glaxo SmithKline and Merck among the companies testing rival vaccines.

While the most advanced version uses the traditional technique of using a weakened form of the live virus, alternative approaches of triggering an immune response using imitations of dengue are also being tested.

Dr Mahoney says: "We do not know whether a live attenuated vaccine will be successful, so it's important that a variety of types are being looked at.

"Even if the Sanofi vaccine goes to market it will only be able to produce enough doses in its first year to meet demand from Brazil alone. We predict the global demand being one billion doses per year."

Dengue may not be considered a global health priority, but this has not prevented important progress from being made to rid the world of the disease.

Dr Lang says: "It is a sign of how far we have come that the World Health Organisation now has a target of halving the death rate and reducing incidence by 25 per cent by 2020.

"This chimes with my personal mantra: dengue – neglected no more!"

A little effort can produce great strides

Interview
John Kufuor
Former president of Ghana

Andrew Jack hears what 50 cents can do

John Kufuor had long been aware of the burden of neglected diseases in Ghana, but it took the visit of a foreign head of state to mobilise his country's government into action.

From river blindness and buruli ulcer to elephantiasis, the country had plenty of health problems that affected its poorest residents. It harboured one of the largest number of cases of guinea worm outside Sudan, a disease energetically targeted for global eradication by former US president Jimmy Carter through his foundation.

"President Carter had visited before I came to power with a technical group of volunteers who targeted guinea worm eradication," Mr Kufuor, the former president of Ghana, recalls. "That focused attention.

"During my tenure, he must have visited four or five times, travelling with a group of experts to some of the remotest parts up in the north. He provided leadership, and we got embarrassed remaining in the capital."

While guinea worm and other diseases were "slow killers" that often escaped attention, he argues: "When the afflicted get relief, they are empowered to work productively. Children can go to school without suffering, to the benefit of the nation.

"In government, the topmost priorities are security and health. If the people are not healthy, they can't be productive and the economy stalls."

Although plenty of attention and funding went to other diseases, led by HIV, over the years, he says: "The truth is that these neglected diseases have been there long before the explosion of HIV. The only difference is they attacked the poorest, marginalised people without a voice.

"The fight must be sustained against HIV, but we want to bring alongside the fight against these other diseases. For as little as 50 cents per person a year, we can make a great onslaught."

He stresses the importance of clean drinking water, and partnerships with non-governmental organisations to help tackle neglected diseases.

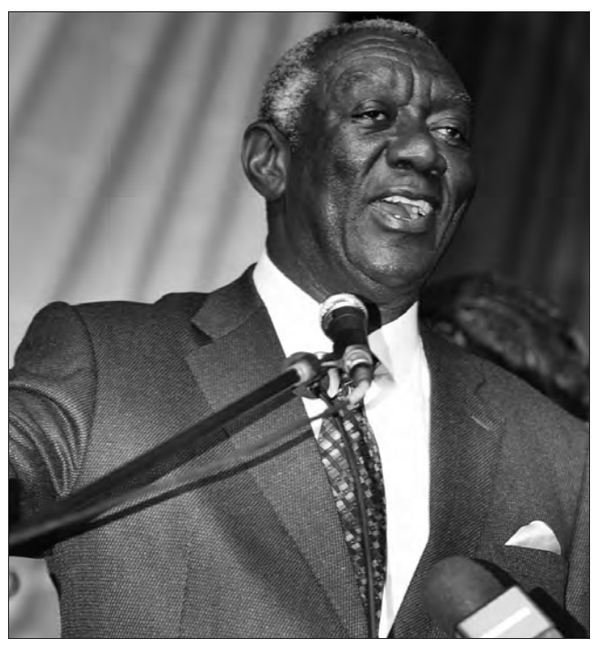
He also cites the broader impact of the pioneering introduction of health insurance in place of the previous out-of-pocket healthcare system dubbed "cash and carry" by critics that offered scant support for the poor. "There is still some way to go, but I believe Ghana is really shaping up," he says.

'If the people are not healthy, they cannot be productive'

Now he is bringing his own gravitas as a former president to try to do the same for his peers across Africa and beyond. This year he was appointed as special envoy to the Global Network for Neglected Tropical Diseases.

Mr Kufuor has spent time both travelling in Africa and meeting donors elsewhere to stress the importance of the cause. But how optimistic is he about fresh support for long unfulfilled pledges to boost health investment across the continent?

"Things are beginning to change. The afflicted tended to be some of the poorest, at the margins of society. Now, with governments getting accountable through democratisation, and the opening up of the world through the IT revolution, governments are having to sit up."



Voice for change: John Kufuor, special envoy AFP

Ruining the mosquito's sex life may pay

Vector control

Work to halt life cycle is promising, says *Clive Cookson*

Genetic modification could be a powerful weapon against the mosquitoes that transmit dengue.

Field trials, involving the release of millions of sterile GM mosquitoes, have given encouraging results in Brazil, Malaysia and Grand Cayman island.

Oxitec, an Oxford university spinout company, developed the technology. A "dominant lethal gene" inserted into the *Aedes aegypti* mosquito enables males to fertilise females – but their larvae die before hatching.

If huge numbers of sterile males are released – at least 10 times more than the wild population – they swamp the native males and mate with all available females, which fail to produce viable offspring.

The large-scale release of male insects sterilised by radiation has been very successful in fighting agricultural pests such as fruitflies, but irradiation does not work with mosquitoes, so Oxitec has pioneered this alternative approach.

The first field trial was carried out two years ago on Grand Cayman in the Caribbean, with results published last month in the journal Nature Biotechnology. The release of 3.3m sterile male mosquitoes over 16 hectares for 23 weeks resulted in an 80 per cent reduction in the number of wild mosquitoes.

Luke Alphey, Oxitec chief scientist, says: "Eighty per cent reduction is an excellent result, especially as wild mosquitoes could migrate into the trial area.

"We should see even stronger reduction in larger or more isolated areas. We believe this approach can be used in many countries to offer a more effective, greener solution to controlling the *Aedes aegypti* mosquito and reducing dengue fever."

Environmental groups dispute the claim that GM insects represent a greener solution to mosquito control. Helen Wallace, director of GeneWatch UK, says the Grand Cayman data were unconvincing.

"Staff would be better employed using the well-established public health approach of removing mosquito breeding sites [water containers] rather than in placing GM mosquito larvae at intervals across a site," she says. "Plans to scale up releases of GM mosquitoes in dengue-endemic Brazil should be halted. Authorities in other places where releases are planned, such as Florida and Panama, would also stop and think again."

80%

Reduction in number of wild mosquitoes during trial

In fact, the technology is gathering momentum in Brazil. Dr Alphey says: "That is where the main action is at the moment."

Oxitec is working with Moscamed, a Brazilian company that already uses radiation-based sterile insect technology to control Mediterranean fruitflies.

In July Moscamed opened a breeding facility where production of Oxitec's GM mosquitoes will be scaled up to produce enough insects for a trial in a town with 50,000 inhabitants.

Although male *Aedes aegypti* mosquitoes do not bite, there were initially some complaints during the Grand Cayman test that the large numbers released were causing a nuisance.

But Dr Alphey says the system was then adjusted to release insects farther from people's homes and to substitute some of the adult mosquitoes with pupae from which adults emerge over a period. No further complaints were received.

While Oxitec is focusing resources on *Aedes aegypti,* scientists believe the technology could also stop *Aedes aldopictus* (Asian tiger mosquito) which is moving aggressively into southern Europe.

It is a secondary vector for dengue and transmits other viruses that threaten human health, including the crippling chikungunya.

On FT.com »

Interactive graphic
Focus on neglected diseases in different parts of the world
www.ft.com/reports

Contributors »

Andrew Jack
Parmaceuticals Correspondent

Clive Cookson
Science Editor

Alan Rappeport
US Consmer Industries Correspondent

Sarah Murray
FT Contributor

Denise Roland
FT Contributor

Ian Moss
Commissioning Editor

Steve Bird
Designer

John Wellings
Picture Editor

For advertising, please contact
Ian Edwards
Phone +44 020 7873 3272
Fax +44 020 7873 4336
Ian.Edwards@ft.com

Projects need co-ordinated approach

Continued from Page 1

disease eradicated, after smallpox. "When a head of state is interested, you can bet the minister of health is interested," he says.

One broader factor mobilising recent efforts has been interest closer to home for donors. Mr Hotez has long highlighted the burden of NTDs, such as helminths and leishmaniasis, in the poor rural and indigenous communities of North America. Caroline Anstey of the World Bank, another important funder, prefers to dub NTDs not neglected diseases, but diseases of neglected people.

Climate change and the growth in commerce means that some diseases – led by mosquito-transmitted dengue – are now moving from poorer to richer emerging countries and into the US and western Europe. No surprise that much pharmaceutical industry investment – and not purely philanthropic support – is going into the search for a vaccine. But many difficulties remain. Sustaining funding – let alone meeting a $2bn gap by 2015 for current international plans – is a particular concern during a period of slower economic growth. Sabin trustee Baroness Hayman, who is keeping a nervous eye on a recent reshuffle in the British government that could change priorities at Dfid, the official development agency, cautions: "We are going to have to work very hard to keep up the momentum on funding. It would be a terrible shame if it went backwards."

Dr Lorenzo Savioli, who runs the NTD programme at the World Health Organisation, says: "Outside the US and the UK, few governments are interested or understood how relevant this is for poverty reduction. We need the eurozone and the yen zone involved."

Prof Alan Fenwick, director of the Schistosomiasis Control Initiative at Imperial College, London, says few African governments yet have their own budget or staff for NTDs. He also says donors should carefully examine the growing number of organisations now competing for support, stressing his own group's low overhead, use of local rather than expatriate staff and careful partnerships to avoid corruption.

These are not neglected diseases but diseases of neglected people

Others call for efficiencies in other ways, including greater linkage between well-established but underfunded NTD programmes and better-supported HIV and malaria projects.

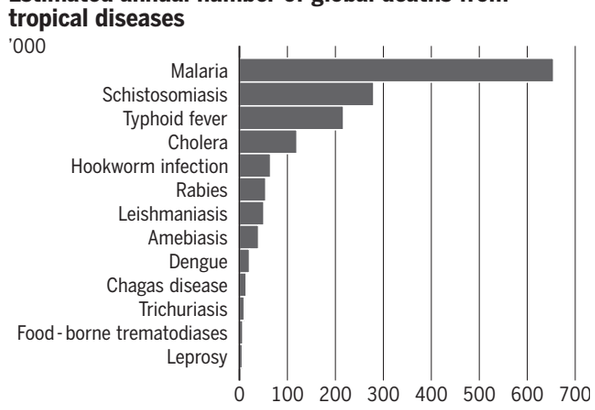
Not all NTDs are receiving equal attention in every country, and nor can they be tackled in the same way. Some are more "tool-ready" than others, though most would benefit from fresh diagnostics and drugs.

"Mass drug administration" – using a number of donated drugs in combination preventatively like a vaccine – is taking off, but remains hindered by poor co-ordination. Some question whether the approach is wise, arguing it may risk triggering drug resistance and placing heavy strains on local communities and health systems.

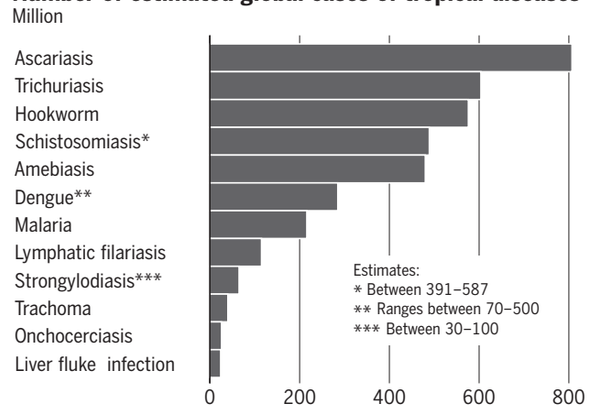
Simon Bush, head of NTDs at Sightsavers, says: "Mass treatments are going well, but if we want to move to elimination we need to look at water, sanitation and hygiene. That's always been the weak link."

Ambitious goals set for eradication of several NTDs in the coming years are unlikely if these issues are not addressed. Medicines can help, but are unlikely to eliminate diseases of poverty alone.

Estimated annual number of global deaths from tropical diseases



Number of estimated global cases of tropical diseases



Source: Peter J. Hotez, The American Society of Tropical Medicine and Hygiene

Waiting for a breakthrough: volunteers for dengue clinical trials at the Ratchaburi hospital near Bangkok, Thailand Sanofi Pasteur

Funds sharpen scientific focus

Research The response to exotic parasites may underpin future cancer treatments, writes *Clive Cookson*

Neglected Tropical Diseases is a convenient name for a disparate group of infections that hardly exist in the developed world but affect more than a billion people in the poorest regions of Africa, Asia and South America. However the label may be misleading in two ways, according to Professor Simon Croft of the London School of Hygiene and Tropical Medicine. First, he says: "Many of the diseases are no longer so neglected."

Medical science is paying more attention to them, helped by increased funding from the pharmaceutical industry, governments and charities. Policy Cures, a health charity that tracks spending on R&D, says $460m was invested on 12 neglected tropical diseases in 2011 – up from $418m in 2010 and just $268m in 2007.

The other reason is the label suggests more similarities between the diseases than exist. Prof Croft, head of the LSHTM faculty of infectious and tropical diseases, says: "Lumping them together conceals their diversity from the viewpoint of medical science. They pose different challenges, and they are at different stages of development when it comes to diagnosis and treatment."

The diseases can be grouped into broad categories, according to the pathogen responsible for the infection and the vector that transmits it. There are four main types of pathogen: helminths (wormlike parasites), trypanosomes (protozoan parasites), bacteria, and viruses. A range of flies, mosquitoes, snails, bugs and other creatures transmit the diseases – and researchers are working on ways to tackle both vectors and pathogens.

Even within each pathogen group, the diseases vary greatly in the way they respond to treatment. Anti-helminthic drugs – mainly derived from veterinary medicines developed to deworm animals – are much more effective against some worms than others. "For some helminthic diseases the cure rate is 90 per cent, for others it is much lower," says Prof Croft.

A particular challenge for scientists fighting helminthic diseases such as onchocerciasis and lymphatic filariasis is to kill the adult worms. Drugs such as Merck's ivermectin can eliminate the larval stages relatively easily but adults can survive and live for many years, producing new larvae that continue to transmit disease.

In addition to chemical drugs, scientists are working on vaccines to block the transmission of tropical diseases. For a few helminthic diseases in which farm animals harbour the infection, inoculation of livestock may be sufficient. But for most diseases new human vaccines are needed – they have been called "anti-poverty vaccines", because they promise to lift people out of hardship by improving their health. New vaccines for the hookworm infections leishmaniasis and schistosomiasis are in early clinical trials, while candidate vaccines for onchocerciasis (river blindness) and Chagas disease are still in pre-clinical research. Most of the vaccine work is being carried out by public sector and non-profit organisations, such as the Sabin Vaccine Institute and Infectious Disease Research Institute in the US. The pharmaceutical industry's involvement is much greater when it comes to the development of new drugs. The funding figures from Policy Cures show a spectacular increase in corporate investment in neglected tropical disease treatments in recent years – from $25m in 2007 to $178m in 2011. This investment has been focused particularly on dengue, which receives more research funding that any other neglected disease.

This year three drug companies – Abbott of the US, AstraZeneca of the UK and Astellas of Japan – signed agreements to collaborate on research with the non-profit Drugs for Neglected Diseases Initiative (DNDi) based in Geneva. AstraZeneca, for example, will provide DNDi with 15,000 chemicals which will be screened at Institut Pasteur Korea for activity against the trypanosomic diseases leishmaniasis, Chagas disease and sleeping sickness. Any "hits" will then be assessed for their potential as starting points for future medicines.

> Most of the vaccine work is carried out by public sector and non-profit groups

Meanwhile significant results continue to emerge from academic research. The latest, published this month in the Biochemical Journal, points the way to a new approach to treating leishmaniasis. Scientists from Edinburgh University in the UK and the US National Institutes of Health have created a chemical that blocks a key enzyme in the parasite responsible for the disease, after testing 300,000 possible drug molecules.

The Leishmania parasite needs the enzyme, pyruvate kinase or PYK, for the glycolysis process that converts sugars into energy. Without it, the parasite dies. What makes the discovery particularly interesting is that it has implications far beyond tropical diseases, neglected or otherwise.

A very similar biological pathway operates in human tumours, which also need PYK to convert food into energy to support their growth, says Hugh Morgan of Edinburgh University. Research into leishmaniasis may therefore also lead to a new way of treating cancer. That would be an unexpected spin-off for research into neglected tropical diseases.

Joint approach is still a dream

Linkage

Synergy would help in tackling diseases, writes *Andrew Jack*

Place a map of the prevalence of HIV in Africa next to one showing the less well known condition of urogenital schistosomiasis, and there is a striking overlap. It is just one example of the broader impact of neglected tropical diseases.

While the connections between many conditions may be poorly studied, the potential for saving money and improving health by co-ordinating the efforts of those fighting them is substantial. Experts argue sharing just a fraction of the generous support to fight the Big Three of HIV, TB and malaria to tackle more neglected diseases could reduce the burden of both sets of conditions.

One measure would be greater support for deworming with drugs already donated. Female genital ulcers caused by schistosomiasis are associated with a substantial increase in transmission of HIV.

And several studies have argued helminth infections increase HIV viral load and the likelihood of mother-to-child transmission. The worms boost the chance of contracting TB, increase the risk any infection will be more severe and less responsive to therapy and also exacerbate anaemia in children and pregnant women, adding to the death toll from malaria.

A second measure would be to enhance malaria bed net distribution by tapping into the infrastructure created by projects such as the Global Programme to Eliminate Lymphatic Filariasis and the African Programme for Onchocerciasis Control.

These community-based initiatives using local volunteers with government support tend to be well accepted compared with intensive one-off malaria bed net campaigns. Using them would increase the likelihood that nets would be used to protect against malaria, while also helping protect from other insect-borne diseases including lymphatic filariasis.

But Prof David Molyneux from the Liverpool School of Tropical Medicine says: "The malaria community does not want to either hear or listen, it seems."

The former head of the Global Alliance to Eliminate Lymphatic Filariasis, he has lobbied over a decade for joint working. As he wrote in the Lancet in 2009: "Although further research might be needed to examine

> The potential for saving money and improving health by co-ordination is substantial

the effect of linking neglected tropical diseases and malaria control on some of the weaker health systems in Africa and elsewhere, we believe that the evidence for combining these two approaches is sufficiently mature to scale up combined neglected tropical disease and malaria control initiatives immediately."

He is still waiting.

The Global Fund to Fight Aids, TB and Malaria, the largest multilateral redistributing funds, said it believed its financing did help strengthen health systems more broadly in recipient countries, allowing them to tackle other conditions. But a spokesman said there was no current direct support: "NTDs do not fall within our mandate."

Poor hit hardest by chronic infections

United States

Tropical diseases can still be deadly in the west, explains *Alan Rappeport*

Impoverished parts of the US remain a hotbed of rare diseases that many Americans have never heard of, with illnesses such as Chagas disease, Leishmaniasis, Trench fever, and Dengue still prevalent.

Appalachia, the Mississippi Delta and poor neighbourhoods in some cities are especially vulnerable, as sanitation and medical supervision is persistently lacking.

"Tens of thousands, or in some cases, hundreds of thousands of poor Americans harbour these chronic infections, which represent some of the greatest health disparities in the United States," Peter Hotez, a professor at The George Washington University and the Sabin Vaccine Institute, wrote in a recent study on the subject.

Neglected diseases are labelled as such because the public has little awareness of them and drug companies do not invest heavily in treatments or vaccines. Public health officials are especially focused on the border region between Mexico and Texas, where neglected tropical diseases such as hookworm and even vivax malaria occur.

One neglected disease that is beginning to get increased attention is Chagas, which some have called the "Aids of the Americas" because of its incubation time and the challenge of finding a cure. According to the Chagas Disease Foundation, the often fatal illness affects up to 20m people in Latin America and has been imported to the US, creating concerns about blood and organ donations.

Chagas is usually transmitted through a triatomine bug, or "kissing bug", according to the US Center for Disease Control (CDC). The bug thrives under poor housing conditions, such as mud walls and thatched roofs, making those living below the poverty line especially vulnerable.

Untreated, Chagas can lead to heart and digestion problems and ultimately death.

The spread of neglected diseases, especially the insect-borne variety, is increasingly problematic because of globalisation, public health experts say.

Michael Osterholm, director of the Center for Infectious Disease Research and Policy at the University of Minnesota, says that increased transport of cargo on ships and aeroplanes is accelerating the spread of infectious diseases.

"We have really eliminated geographic barriers with the modern transportation system we have," Mr Osterholm says. "We are moving mosquitoes around the world every day in cargo."

The increased speed of travel is exacerbating this effect, Mr Osterholm says, pointing to the quick spread of swine flu in 2009, which became a public health scare.

The efficiency of the pharmaceutical sector's supply chain has also been shown to have drawbacks when it comes to faulty medicine. A bad batch of methylprednisolone acetate is believed to have led to an outbreak of fungal meningitis just this month.

> **169**
> **Number of West Nile virus related deaths in the US**

The injectable steroid that is used to treat back pain was thought to have originated in a compounding pharmacy in Massachusetts and quickly spread to sicken people in six states, killing five.

Meanwhile, outbreaks such as the West Nile virus in several states and Hantavirus in Yosemite National Park have raised awareness that rare diseases can still be deadly in the US. Earlier this month the CDC said there had been 169 West Nile virus-related deaths so far this year and nearly 4,000 cases. That puts 2012 on pace to be the worst year for the virus since 2003.

Many experts argue that global warming is to blame for the spread of West Nile. At a press conference in August, Lyle Petersen, director of the CDC's division of vector-borne infectious diseases, said the unusually hot summer had "fostered conditions favourable to the spread of West Nile virus to people".

Triatoma dimidiata: a blood-sucking insect that spreads Chagas disease AFP

Combating Neglected Diseases

Tide may be turning against guinea worm

Eradication Simple, practical steps involving communities have been vital in the fight against this debilitating parasite, says *Sarah Murray*

With cases of guinea worm disease down from 3.5m in 21 countries in 1986 to a matter of hundreds in four African countries today, the near eradication of this painful and debilitating disease is being celebrated as a global health success story. However, unlike many disease eradication programmes, no drugs or immunisations were available. Progress in this fight has depended on aggressive advocacy efforts at every level of society.

Guinea worm disease, dracunculiasis, is a parasitic disease that spreads when people drink contaminated water containing a water flea that is host to the guinea worm larvae.

These larvae hatch in the digestive tract and, roughly a year later, the worm – which can be up to 120 centimetres long – emerges from the body, often through the lower limbs.

In an attempt to relieve the excruciating pain and burning sensation caused as the worm exits their bodies, people immerse themselves in water, at which point it releases thousands more larvae. Anyone drinking from this water source becomes infected.

What makes the disease difficult to battle is no symptoms are apparent in the sufferer until the fully grown worm emerges from the body.

In addition, health workers face logistical problems. Dieudonné Sankara, an epidemiologist in the World Health Organisation's guinea worm eradication programme, says: "This disease occurs in places that are very remote. It's very difficult to make contact with these people – there's no access, no roads and they are very neglected."

However, in the campaign's early stages the challenge lay closer to home – convincing health ministries and international agencies that this was a battle worth fighting.

Donald Hopkins, vice-president of health programmes at Carter Center, the human rights group that has led efforts to eradicate guinea worm, says: "The disease was so obscure. It was in the back of beyond and people weren't paying attention to it."

Moreover, in the 1980s, when efforts to eliminate guinea worm began, the World Health Organisation had recently declared smallpox eradicated – a victory that coincided with shifting priorities in global health policy.

Drawn out: the fight to banish the worm has been a long one AFP

Dr Hopkins says: "Single-disease eradication had gone out of fashion.

"The mantra in the early days of the guinea worm programme was primary healthcare and an integrated approach that would provide health for all by the year 2000 – that was an impediment to getting the focus on to guinea worm eradication."

Having convinced governments and agencies that guinea worm could – and should – be eradicated, the next challenge was persuading affected communities to change behaviour.

While temephos, a larvicide, can be used to treat water, killing the fleas that host the larvae, the primary strategy is ensuring people living in endemic areas do not drink contaminated water and, if infected, do not bathe in water used for drinking.

Dr Sankara says: "That's easy to say, but difficult to do." The strength of traditional local beliefs has not helped. Affected communities often saw the disease as a curse or affliction over which they had no control.

Dr Hopkins says: "They didn't like having guinea worm but thought they understood why they had it. They did not understand that it was coming from their drinking water and that it was in their power to do something about it – people coming from the outside often underestimated the strengths of those traditional beliefs."

This has meant showing people how the disease spreads and persuading them to distrust all water sources except those they know to be clean.

In this respect, a powerful tool is a simple glass jar, used to scoop water from contaminated ponds and demonstrate to onlookers what it contains.

Convincing affected communities to take action to help themselves has also been critical. Dr Hopkins says: "The unsung heroes in all of this were the village volunteers, who were willing and able to help educate their neighbours,"

Yet while guinea worm is poised to be the next human disease after smallpox to be eradicated, the last stages of the battle will be the toughest. Because of the way the disease spreads, one case can lead to dozens, with symptoms only appearing a year or more after infection.

This means employing a strategy Dr Hopkins calls "redundant surveillance". With cash for anyone reporting a confirmed case, everyone in the community becomes a surveillance agent.

> Convincing affected communities to take action to help themselves has also been critical

And because the offer of cash can create reporting incentives, generating false positives, absence of reported cases over a certain period can be accepted with greater confidence (to be declared free of guinea-worm, a country must report no indigenous cases, through active surveillance, for at least three calendar years).

This community-based strategy has lessons to offer those running many kinds of health campaigns.

Dr Sankara says: "What we're doing will shape other programmes in the years to come.

"And, for guinea worm disease eradication, one critical thing has been using local manpower and empowering communities to take care of their own health."

A shared way forward offers hope

Research

Global co-operation may provide many of the answers, writes *Andrew Jack*

When Eisai signed up late last year to a new international system designed to share details of its library of experimental drug compounds with external researchers tackling neglected diseases, it soon sparked interest.

It quickly became not only the first Japanese pharmaceutical group to join the Re:Search initiative of the World Intellectual Property Organization, but one of the first to formally claim a successful match (albeit negotiations were already under way before it joined).

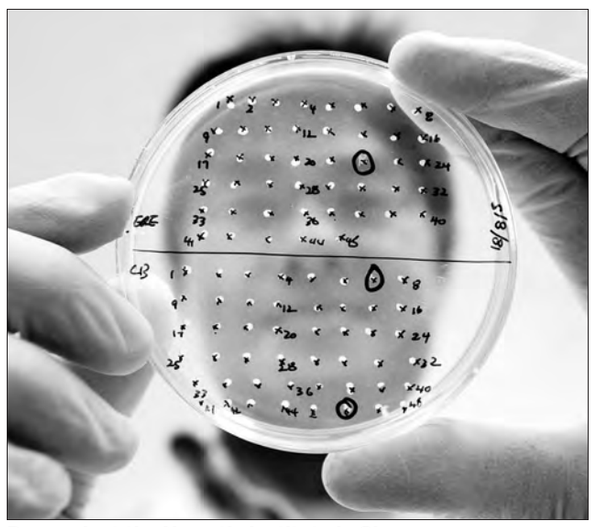
The company handed over details of seven compounds which it believed had potential value, including E6020. Last month, the Sabin Vaccine Institute in the US signed a deal to test its value as an adjuvant to boost the immune response to two of its experimental vaccines, for Chagas disease and leishmaniasis.

"Adjuvants are super hard to come by because they are closely guarded by the major vaccine manufacturers," says Peter Hotez, president of the Sabin Institute.

"It's a real hurdle in the vaccine space to have access to adjuvants. It's something we struggle with for each of our vaccines, so it's great that Eisai provided that access."

Re:Search is the latest in a series of such multi- and bilateral initiatives designed to "crowd source" and pool international expertise in the effort to boost neglected disease research. Companies share information and agree to license any compounds, charging no royalty in their use in research and none for their eventual commercialisation in the world's least developed countries.

Some companies have pursued neglected disease research in-house, including Novartis through its specialist tropical disease institute in Singapore and GlaxoSmithKline (GSK) in Spain. But a number, including both GSK and Pfizer have opened their internal drug compound libraries to outside academics in the hunt for neglected disease treatments.



Research at the Novartis Institute in Singapore Bloomberg

Others have formed public-private partnerships, combining expertise and funding with additional donor support, such as the Drugs for Neglected Diseases Initiative, which originally regarded co-operation with the pharmaceutical industry with suspicion, but has since signed up to work with a number of companies for different diseases.

So far, the output of such non-profit product development partnerships – most focused on a single disease – has been modest, often picking "low hanging fruit" such as fixed-dose combinations of existing therapies or reformulations to make them easier to take. That partly reflects the lengthy periods required for drug and vaccine testing.

It also highlights the difficulties of finding the funding for costly research, with a surge in costlier late-stage trials just as austerity bites. Paul Herrling from Novartis has proposed a new hybrid model that would pool donor support across a range of diseases and organisations, with an expert committee deciding the most merit-worthy project across a wide-ranging portfolio.

That has met resistance from different funders and scientists reluctant to give up their own preferred projects, and questioning the qualifications of such a broader expert group. But for many diseases for which treatments remain ineffective, greater research co-operation still will be required if much further progress is to be made.

Companies strive for better outcomes from donations

Corporate efforts

Big pharma is stepping up efforts to aid poorer nations, says *Andrew Jack*

Roy Vagelos took a historic decision nearly four decades ago that paved the way for a new era in efforts to tackle neglected tropical diseases. It set a high standard not only for his company but the entire pharmaceutical sector in drug donations for the poor.

In 1975 when Bill Campbell, a researcher at Merck in the US, saw during tests in the laboratory that his company's drug ivermectin for deworming cattle had the potential to work in humans, he had gone to Mr Vagelos, the then head of research, who authorised the costly and lengthy clinical trials to prove it.

By the time the results finally demonstrated that it was safe and effective in treating onchocerciasis – river blindness – a dozen years later, Mr Vagelos had stepped up to become Merck's chief executive.

He bounced his own board into an unprecedented pledge: free supplies of the drug (branded as Mectizan) for as long as it was needed for the disease, backed with funding through a partnership for its distribution.

Brenda Colatrella, head of corporate responsibility, says: "Merck didn't have a presence where those populations lived in some of the remotest parts of Africa and Latin America, and those who needed it couldn't afford to buy it at any price."

Her department oversees a programme that this month is celebrating its 25th year, with more than 1bn treatments provided.

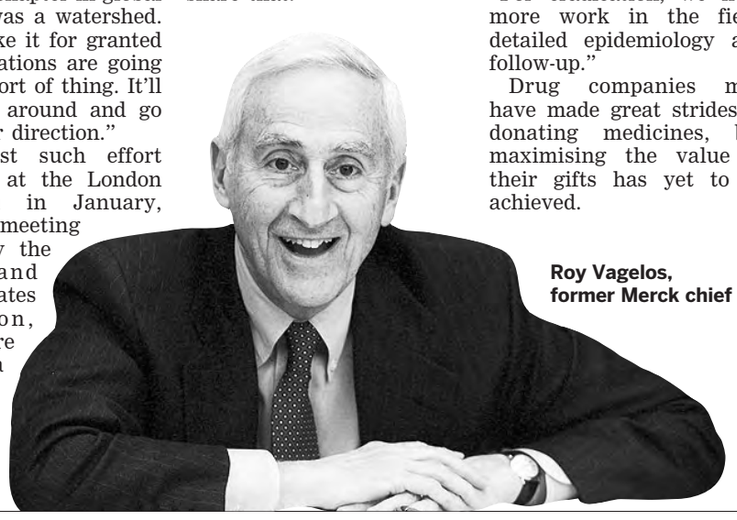
Bill Foege, a health expert credited with devising the strategy that led to the eradication of smallpox, helped plan the programme.

He says: "It launched an entire new chapter in global health. It was a watershed. We now take it for granted that corporations are going to do this sort of thing. It'll never turn around and go in the other direction."

The latest such effort took place at the London Declaration in January, during a meeting initiated by the Bill and Melinda Gates Foundation, when more than a dozen pharmaceutical companies stepped up donations of drugs to help eliminate a series of neglected diseases.

Taking part was Merck of Germany, which agreed to raise its annual donation of praziquantel tablets for the schistosomiasis parasite from 25m to 250m.

Sir Andrew Witty, chief executive of GlaxoSmith Kline, which has pledged unlimited supplies of albendazole from new production lines to treat helminths and lymphatic filariasis, says: "This is an extremely human issue. When you are a company that, through hard work, good fortune and luck, has control and insight into certain technologies, and a talent base to apply and develop it, it's our job to figure out how to share that."



Roy Vagelos, former Merck chief

But such donations are only the start. Distribution remains difficult, notably in trying to ensure a series of drugs from different companies arrive together to be handed out in local community campaigns.

Andy Wright, director of GSK's disease programme, says: "There are lots of complaints on the ground that co-ordination is not right yet, although the direction of travel is right."

Adrian Hopkins, his counterpart at Merck, also points to concern about "orphan" countries such as the Central African Republic, where few large donors are present to provide support and distribution. He also cautions that more monitoring will be required: "For eradication, we need more work in the field, detailed epidemiology and follow-up."

Drug companies may have made great strides in donating medicines, but maximising the value of their gifts has yet to be achieved.

Glory days for a plan to reward research hover in the distance

Priority review vouchers

Scheme designed to encourage research has had few takers, says *Andrew Jack*

It took several years to move from academic idea through the political process to the drafting of regulatory small-print, but an innovative funding model for research into neglected diseases has finally come of age. The "priority review voucher" provides incentives to companies to discover treatments, however uptake so far has been slow.

A law in 2007 in the US paved the way for the voucher, inspired by a simple idea: the prospect of earlier launch and greater sales of a "mainstream" drug by a pharmaceutical company could persuade them to develop treatments for neglected tropical diseases, on which the financial returns are scant.

For any neglected disease treatment approved by the US Food and Drug Administration, companies can now receive an accelerated decision – within six months – on the safety and efficacy of any other experimental medicine in their pipelines, potentially halving the usual deadline of 10 months or more after submission.

Rather than extending the expiry date of a patent, the voucher offers the prospect of a front-loaded extension by launching several months earlier than usual.

David Ridley, associate professor at Duke University Fuqua School of Business, and one of those who first described the concept of the voucher in 2006, estimates the value at $200m-300m.

In practice, only one voucher has so far been issued and that in unusual circumstances: it was granted in 2009 to Novartis of Switzerland for Coartem, a highly effective malaria drug that had already been approved by the FDA and regulators internationally and was used across Asia and Africa. It took a further two years before the company decided how to redeem it, seeking accelerated review for Ilaris, its experimental treatment for gouty arthritis. While the regulators honoured their deadlines, they ultimately ruled against approving the drug, rendering the voucher worthless.

> The voucher offers the prospect of launching a drug earlier than usual

Novartis said it chose Ilaris "because of the significant unmet need" and refused to comment on the outcome.

"I'm not disappointed and I'm not surprised," says Mr Ridley. "The value is not a huge amount for big pharma, but we hope the voucher will nudge some of them. It is one of many mechanisms and still has great potential." He points out that revised US regulatory legislation this year has extended a similar voucher to rare paediatric cancers, reducing the application fee and cutting the notice period required by a company signalling its intention to file for a priority review.

He hopes similar changes will apply to neglected diseases, and that the definition will be extended to other ailments previously excluded, including tropical disease Chagas. In a survey last month of drug developers, Bio Ventures for Global Health, a non-profit group encouraging research for neglected diseases, suggested the voucher was a useful incentive.

The FDA proved that it respected the terms, even if Coartem was an unusual case and Ilaris ultimately failed to benefit.

With five vaccines and three drugs in late-stage clinical trials that could be eligible, the voucher's best days may yet be ahead.